

Remarks

With the cancellation of claims 4, 16, 18 and 24, claims 1-3, 5-11, 13-15, 17, 19-23 and 25-37 are pending.

The amendment to claim 6 is supported by claim 16 as filed and the knowledge in the art that, among the solvents (water, methanol, ethanol, propanol, acetonitrile, acetone, tetrahydrofuran, dimethylformamide, dimethyl sulfoxide and isobutyl methyl ketone) listed in page 12, lines 29-31 of the specification and recited in claim 6, water, methanol, ethanol and propanol are anti-solvents of bicalutamide. The new claim 38 is supported by the specification at page 13, lines 26-27.

The amendment to claim 23 is supported by the specification at page 14, lines 17-21.

Claim 21 has been made independent of claim 13, and there is no narrowing of the scope of claim 21.

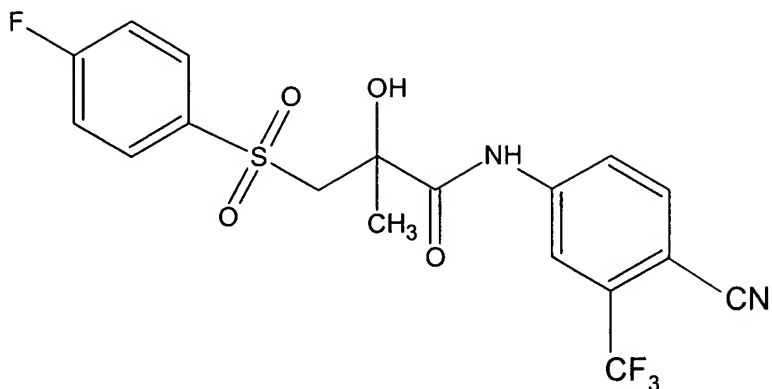
The amendment to claim 29 would not narrow the scope of the amended claim recitation because a person of skill in the art would have understood that “solvent” in claim 29 as filed refers to the first solvent because the first solvent is in step (i) of claim 23.

The replacement of “THF” and “DMF” with “tetrahydrofuran” and “dimethylformamide”, respectively, in the claims would not narrow the scope of the amended claim recitations because the amendments merely replace commonly accepted acronyms with the commonly accepted chemical names.

Claim Rejections -- 35 U.S.C. 103

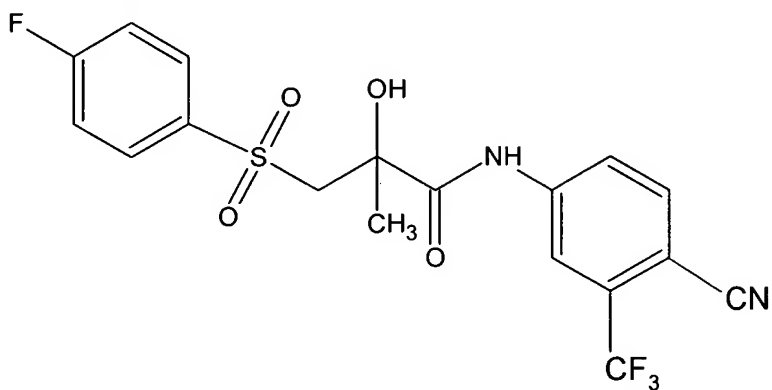
Applicants respectfully traverse the obviousness rejection of claims 1-11 and 13-32 over Ekwuribe (US 6,479,692, hereinafter US ‘692), Tucker (US 4,636,505) and Keil et al (US 5,300,652) and further in view of Gold (US 3,875,229).

The processes of claims 1-11 and 13-32 involve the crystallization of bicalutamide having the following chemical structure:



bicalutamide

US '692 discloses crystallizing bicalutamide from a mixture of ethyl acetate and petroleum ether (see Example 2, column 13, lines 55-57).



Chemical: bicalutamide

Crystallization Solvents: mixture of ethyl acetate and petroleum ether

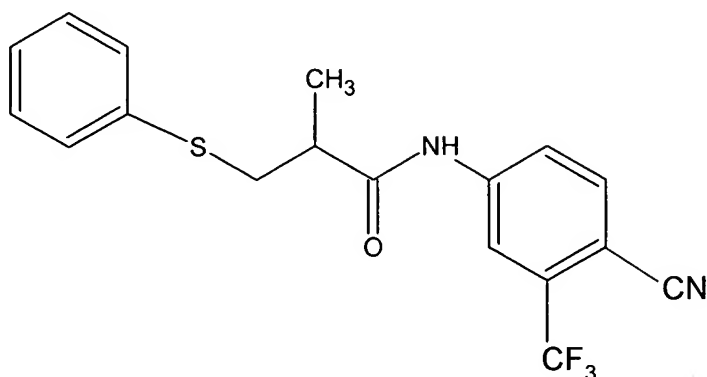
Reference: US '692 (Example 2)

US '692 differs from claims 1-11 and 13-33 in not teaching the use of the solvents recited therein for crystallizing bicalutamide.

Claims 2, 10 and 32 further differ from US '692 in that US '692 fails to disclose seeding in the bicalutamide crystallization procedure.

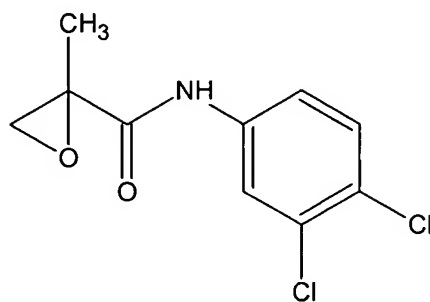
The Office Action attempts to rely on Tucker, Keil et al and Gold to remedy the differences between the claims and US '692. However, as explained below, the attempt failed.

The Office Action states that Tucker uses two different solvents. Applicants note that Tucker discloses a genus of acylanilides which includes bicalutamide (see Abstract), but Tucker does not describe any specific solvent to crystallize bicalutamide. Tucker discloses the use of a mixture of toluene and petroleum ether to crystallize 4-cyano-3-trifluoromethyl-N-(2-hydroxy-2-methyl-3-phenylthiopropionyl)aniline (Example 1, column 8, lines 29-30) having a chemical structure shown below.



Chemical: 4-cyano-3-trifluoromethyl-N-(2-hydroxy-2-methyl-3-phenylthiopropionyl)aniline
Crystallization Solvents: mixture of toluene and petroleum ether
Reference: Tucker (Example 1)

Tucker also discloses using petroleum ether to crystallize 3,4-dichloro-N-(2,3-epoxy-2-methylpropionyl)aniline (Example 3, column 11, lines 57-59) having a chemical structure shown below.



Chemical: 3,4-dichloro-N-(2,3-epoxy-2-methylpropionyl)aniline
Crystallization Solvent: petroleum ether

Reference: Tucker (Example 3)

The chemical structures of Examples 1 and 3 are different from that of bicalutamide. In addition, the organic solvents used by Tucker to crystallize Example 1 or 3 do not contain water, methanol, ethanol, propanol or isopropanol as required by the instant claims. The petroleum ether or the mixture of toluene and petroleum ether used by Tucker are non-polar aprotic solvents (see a copy of www.cem.msu.edu/~reusch/OrgPage/solvent.htm attached taken from the organic chemistry website of the Michigan State University; a copy of which is attached). In contrast, water, methanol, ethanol, propanol and isopropanol are polar protic solvents.

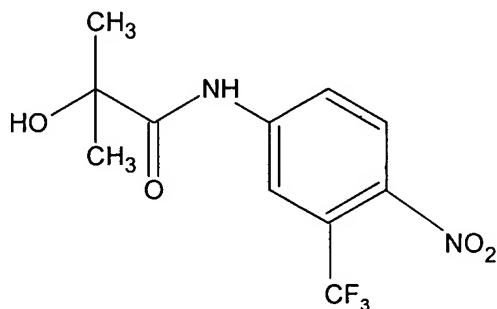
The Office Action states that “applicants are claiming a simple crystallization process, which is well known in the organic chemistry.” (page 2, the last paragraph, of the Office Action). The Office Action also indicates that, although US ‘692 teaches using only a mixture of ethyl acetate and petroleum ether to crystallize bicalutamide, “it does not mean that one of ordinary skill in the art would not have used other solvents for crystallization, because the crystallization using claimed solvents is well known in the art, and a mere fact that US ‘692 has not used those solvents, does not preclude one of ordinary skill in the art to not to use those solvents.”

Applicants want to emphasize that the key issue is not whether one of ordinary skill in the art would be precluded from using the solvents recited in the claims. The key issue for the obviousness rejections in this case is whether one of ordinary skill in the art would have been motivated to modify the teachings of US ‘692 using the disclosures in the secondary prior art cited by the Office Action in order to use the solvent(s) recited in the claims to crystallize bicalutamide. Applicants contend that the Office Action has not put forth any motivation or desirable reason for a person of ordinary skill in the art to replace the mixture of ethyl acetate and petroleum ether with the solvent(s) recited in the instant claims. US ‘692 and the secondary prior art references do not disclose or suggest using the solvent(s) recited in the instant claims to crystallize bicalutamide.

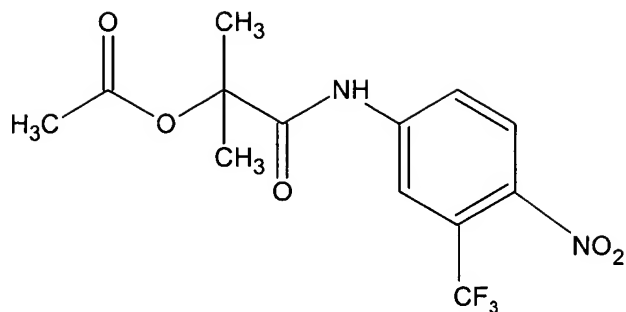
The Office Action appears to take a position that it would have been obvious to modify the crystallization process of US ‘692 by using the solvents recited in the claims merely because (a) the crystallization process claimed is simple and well known in organic chemistry, and (b) crystallization using the solvents recited in the claims are well known in the art. Applicants

respectfully disagree. The Examiner's attention is directed to an attached copy of a portion of the Handbook for Organic Chemistry Lab taken from the website of the University of Colorado attached (<http://orgchem.colorado.edu/hndbksupport/cryst/cryst.html>), which states that "successful crystallization relies on a blend of science and art; its success depends more on experimentation, observation, imagination, and skill than on mathematical and physical predictions." Thus, crystallization of compounds is not as simple as alleged by the Office Action. A person of ordinary skill in the art would recognize that there is no reasonable expectation that replacing the mixture of ethyl acetate and petroleum ether with the solvent(s) recited in the instant claims would succeed in crystallizing bicalutamide. The solvents disclosed by the secondary references relied upon by the Office Action were for crystallizing compounds having chemical structures different from that of bicalutamide. It could not be reasonably predicted that the same solvents, albeit known solvents, used by the secondary references would succeed in crystallizing bicalutamide.

The Office Action states that Gold uses additional solvents such as isopropyl ether, hexane, benzene and methanol, and mixture thereof. Applicants note that Gold does not disclose bicalutamide or any genus of compounds that includes bicalutamide. Gold discloses the crystallization of the following anilide compounds using the solvents described below (see Example 2, column 9, lines 55-56; Example 4, column 10, lines 61-62; Example 5, column 11, lines 11-12; Example 6, column 11, lines 26-27; and Example 7, column 11, lines 40-41):



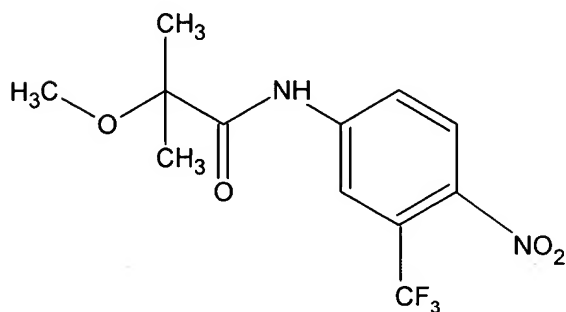
Chemical: 2-hydroxy-4'-nitro-3'-trifluoromethylisobutyranilide
Crystallization Solvents: mixture of benzene and methanol
Reference: Gold (Example 2)



Chemical: 2-acetoxy-4'-nitro-3'-trifluoromethylisobutyranilide

Crystallization Solvents: mixture of benzene and hexane

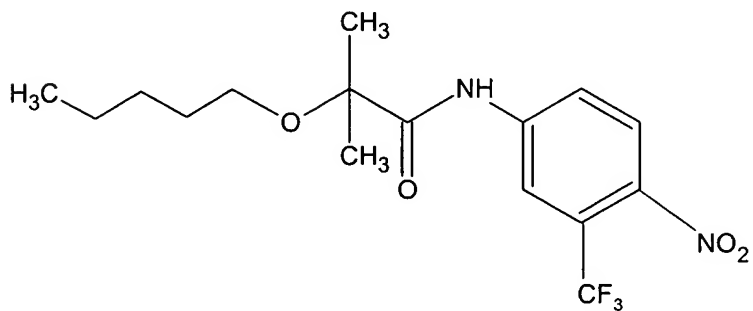
Reference: Gold (Example 4)



Chemical: 2-methoxy-4'-nitro-3'-trifluoromethylisobutyranilide

Crystallization Solvent: isopropyl ether

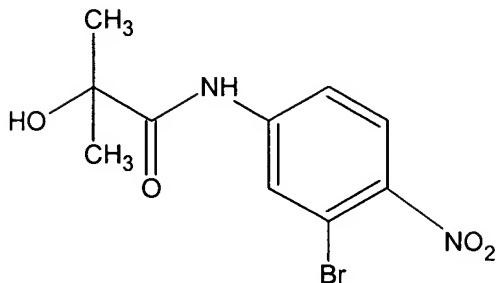
Reference: Gold (Example 5)



Chemical: 2-valeryloxy-4'-nitro-3'-trifluoromethylisobutyranilide

Crystallization Solvent: isopropyl ether

Reference: Gold (Example 6)



Chemical: 2-hydroxy-3'-bromo-4'-nitroisobutyranilide

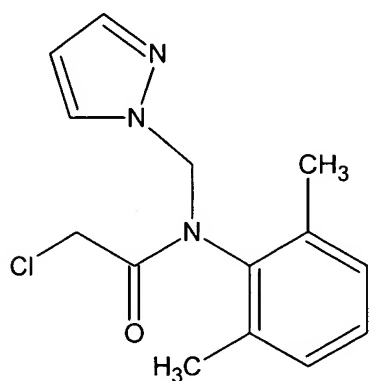
Crystallization Solvent: benzene

Reference: Gold (Example 7)

Benzene, hexane and isopropyl ether used by Gold are non-polar aprotic solvents (see www.cem.msu.edu/~reusch/OrgPage/solvent.htm from the Michigan State University). But water, methanol, ethanol, propanol or isopropanol recited in the instant claims are polar protic solvents. Even though Gold used a mixture of benzene and methanol to crystallize Example 2, the chemical structures of Gold's Example 2 and bicalutamide are different. The Office Action indicates that inasmuch as the functional group is anilido, a person of ordinary skill in the art would be motivated to use solvents of the prior art in the crystallization of any anilido compounds (see page 3 of the Office Action). Applicants respectfully disagree. As pointed out above, crystallization of compounds is not as simple as alleged by the Office Action. In addition to the amido group, different anilido derivatives have other functional groups and different hydrocarbon skeleton, both of which can affect the crystallization of the anilido derivatives by contributing differently in hydrogen bonding and/or van der Waals interaction. The Gold's Example 2 differs from bicalutamide at least in (1) not having a 4-fluorophenylsulfonyl substitution on the gamma carbon of the amide group, and (2) having a nitro instead of cyano substituent at the 4-position of the aniline group. These differences in chemical structures would make it difficult to predict that the mixture of benzene and methanol used by Gold in Example 2 would succeed in crystallizing bicalutamide. This is one of the reasons why a person of ordinary skill in the art would not be motivated by Gold to use the mixture of benzene and methanol to crystallize bicalutamide.

In addition, comparison of the chemical structures of Examples 2, 4, 5 and 6 of Gold, all of which are 4'-nitro-3'-trifluoromethylisobutyranilide derivatives, shows a trend in that as the left end of the molecule becomes bulkier (Examples 4-6 versus Example 2), Gold shied away from using protic methanol but concentrated in using non-polar aprotic benzene, hexane and isopropyl ether. This is another reason why a person of ordinary skill in the art would not be motivated by Gold to use methanol to crystallize bicalutamide.

The Office Action states that Keil et al uses various solvents for crystallization of an anilide with or without seeding. Applicants note that Keil et al is related to the crystallization of 2-chloro-(2',6'-dimethyl-N-pyrazol-1-ylmethyl)-acetanilide, i.e. an acylanilide derivative (see Abstract and column 1, lines 51-52). But as shown below, the chemical structure of the acylanilide of Keil et al is different from that of bicalutamide at least in a number of ways:



2-chloro-(2',6'-dimethyl-N-pyrazol-1-ylmethyl)-acetanilide of Keil et al

(1) the acylanilide of Keil et al has 2,6-dimethyl substituents on the anilido phenyl ring, while bicalutamide has 3-trifluoromethyl-4-cyanol substituents; (2) the amido nitrogen atom of the acylanilide of Keil et al is substituted with a pyrazolylmethyl group, while the amido nitrogen atom of bicalutamide is unsubstituted; and (3) the beta carbon atom of the acylanilide of Keil et al is merely substituted with chloro, but the beta carbon atom of bicalutamide is substituted with methyl, OH and 4-fluorophenylsulfonylmethyl groups.

With these structural differences, applicants submit that a person of ordinary skill in the art would not have used the disclosure of Keil et al to modify the process of US '692 in view of Tucker and Gold to arrive at the claimed processes.

Withdrawal of the obviousness rejections is requested.

Obviousness Type Double Patenting Rejection

Applicants respectfully traverse the obviousness type double patenting rejection of claims 34-37 over claims 1-7 of U.S. Patent No. 6,797,843 (hereinafter US '843) in view of Ekwuribe et al (US '692) or Keil et al. However, to advance prosecution, a terminal disclaimer would be filed if at least one of other claims is found to be allowable. Applicants request that the obviousness type double patenting rejection be held in abeyance.

In the event that this Amendment is deemed not timely, applicants petition for an appropriate extension to time. The petition fee, and any other fees that may be required in relation to this Amendment, can be charged to Deposit Account No. 11-0600. The Examiner is urged to call the undersigned in the event that there remains any minor issues that can be resolved with a telephone interview.

Respectfully Submitted,
KENYON & KENYON

Dated: August 29, 2005

By: King L. Wong
King L. Wong
(Reg. No. 37,500)

Enclosures: a copy of www.cem.msu.edu/~reusch/OrgPage/solvent.htm;
a copy of www.cem.msu.edu/~reusch/OrgPage/solvent.htm

1500 K Street, N.W.
Washington, DC 20005
(202) 220-4223

This page has tables of data for aprotic solvents and protic solvents.
--

Aprotic Solvents^a

Name (abbrev.)	Formula	Mol.Wt.	ϵ	b.p. ^b	m.p.	density ^c	Ref. Index ^c
perfluorohexane	$\text{CF}_3(\text{CF}_2)_4\text{CF}_3$	338		59 °C	-4 °C	1.669	1.2515
α,α,α -trifluorotoluene	$\text{CF}_3\text{-C}_6\text{H}_5$	146.1		103°	-29°	1.189	1.4140
pentane (Pent)	$\text{CH}_3(\text{CH}_2)_3\text{CH}_3$	72.2	1.84	36 °	-130 °	0.626	1.3575
hexane (Hex)	$\text{CH}_3(\text{CH}_2)_4\text{CH}_3$	86.2	1.88	69°	-95°	0.659	1.3749
cyclohexane (Cy)	C_6H_{12}	84.2	2.02	81°	6.5°	0.779	1.4262
methylcyclohexane	$\text{CH}_3\text{-C}_6\text{H}_{11}$	98.2	2.02	101°	-127°	0.769	1.4231
decalin [c + t]	$\text{C}_{10}\text{H}_{18}$	138.3	2.15	192°	-124°	0.887	1.4758
dioxane	$\text{C}_4\text{H}_8\text{O}_2$	88.1	2.21	101°	11.8°	1.034	1.4224
carbon tetrachloride	CCl_4	153.8	2.24	77°	-23°	1.584	1.4164
freon-11	CFCl_3	137.4	2.28	24°	-111°	1.494	1.3821
benzene (PhH)	C_6H_6	78.1	2.28	80°	5.5°	0.879	1.5011
toluene	$\text{CH}_3\text{-C}_6\text{H}_5$	92.1	2.38	111°	-95°	0.867	1.4970
triethyl amine	$(\text{C}_2\text{H}_5)_3\text{N}$	101.2	2.42	90°	-115°	0.728	1.4010
carbon disulfide	CS_2	76.1	2.64	46°	-112°	1.270	1.6280
diisopropyl ether	$[(\text{CH}_3)_2\text{CH}]_2\text{O}$	102.2	3.88	68°	-86°	0.724	1.3681
diethyl ether (ether)	$(\text{C}_2\text{H}_5)_2\text{O}$	74.1	4.34	35°	-116°	0.713	1.3524
t-butyl methyl ether (MTBE)	$(\text{CH}_3)_3\text{COCH}_3$	88.2		55°	-109°	0.740	1.3686
chloroform	CHCl_3	119.4	4.81	61°	-64°	1.480	1.4429
ethyl acetate	$\text{CH}_3\text{CO}_2\text{C}_2\text{H}_5$	88.1	6.02	77°	-84°	0.901	1.3724
1,2-dimethoxyethane (glyme)	$\text{CH}_3\text{OCH}_2\text{CH}_2\text{OCH}_3$	90.1	7.20	84°	-58°	0.867	1.3800
2-methoxyethyl ether (diglyme)	$(\text{CH}_3\text{OCH}_2\text{CH}_2)_2\text{O}$	134.2		160°	-68°	0.944	1.4097
tetrahydrofuran (THF)	$\text{C}_4\text{H}_8\text{O}$	72.1	7.58	66°	-109°	0.889	1.4072
methylene chloride	CH_2Cl_2	84.9	8.93	40°	-95°	1.317	1.4242
pyridine (Py)	$\text{C}_5\text{H}_5\text{N}$	79.1	12.4	115°	-42°	0.983	1.5102
2-butanone (MEK)	$\text{CH}_3\text{COC}_2\text{H}_5$	72.1	18.5	80°	-87°	0.805	1.3788
acetone	CH_3COCH_3	58.1	20.7	56°	-95°	0.790	1.3587
hexamethylphosphoramide	$\text{C}_6\text{H}_{18}\text{N}_3\text{PO}$	179.2	30.0	235°	7°	1.028	1.4588

N-methylpyrrolidinone	C ₆ H ₉ NO	99.1	32.0	202°	-24°	1.028	1.4700
nitromethane	CH ₃ NO ₂	61.0	35.9	101°	-29°	1.138	1.3812
dimethylformamide	HCON(CH ₃) ₂	73.1	36.7	153°	-60°	0.949	1.4305
acetonitrile	CH ₃ CN	41.1	37.5	82°	-44°	0.782	1.3441
sulfolane	C ₄ H ₈ SO ₂	120.2	43.3	287°	28.5°	1.262	1.4820
dimethyl sulfoxide	(CH ₃) ₂ SO	78.1	46.7	189°	18.5°	1.096	1.4783
propylene carbonate	C ₄ H ₆ O ₃	102.1	64	240°	-55°	1.189	1.4210

a) listed by increasing
dielectric constant ϵ

(b) boiling point at 760 torr

(c) most values for 20 °C

Organic Chemistry
Michigan State UniversityProtic Solvents^a

Name (abbrev.)	Formula	Mol.Wt.	ϵ	b.p. ^b	m.p.	density ^c	Ref. Index ^c
propionic acid	CH ₃ CH ₂ CO ₂ H	74.1	3.44	141 °C	-21 °C	0.993	1.3865
diethyl amine	(CH ₃ CH ₂) ₂ NH	73.1	3.58	55°	-50°	0.707	1.3854
butyl amine	CH ₃ (CH ₂) ₃ NH ₂	73.1	4.88	77°	-49°	0.739	1.4014
propyl amine	CH ₃ (CH ₂) ₂ NH ₂	59.1	5.31	49°	-83°	0.717	1.3882
acetic acid	CH ₃ CO ₂ H	60.1	6.15	118°	17°	1.049	1.3719
trifluoroacetic acid (TFA)	CF ₃ CO ₂ H	114.0	8.55	72°	-15°	1.489	1.2850
phenol	C ₆ H ₅ OH	94.1	9.78	182°	41°	1.054	1.4746
isopropyl alcohol	(CH ₃) ₂ CHOH	60.1	19.9	82°	-88°	0.785	1.3772
ammonia (anhyd.)	NH ₃	17.0	22.4	-33°	-78°	0.685	1.325
ethanol (ethyl alcohol)	CH ₃ CH ₂ OH	46.1	24.6	78°	-114°	0.789	1.3614
2,2,2-trifluoroethanol	CF ₃ CH ₂ OH	100	26.5	79°	-44°	1.393	1.2907
methyl alcohol	CH ₃ OH	32.0	32.7	65°	-98°	0.791	1.3284
ethylene glycol	HOCH ₂ CH ₂ OH	62.1	37.7	197°	-13°	1.114	1.4318
glycerol	HOCH ₂ CH(OH) CH ₂ OH	92.1	42.5	290°	18°	1.261	1.4746
formic acid	HCO ₂ H	46.0	58.5	101°	8.3°	1.220	1.3714
water	H ₂ O	18.0	80.2	100°	0.0°	0.998	1.3330
formamide	HCONH ₂	45.0	109	211°	2.6°	1.133	1.4475

a) listed by increasing

(b) boiling point at 760 torr

(c) most values for 20 °C

Organic Chemistry

dielectric constant ϵ

Michigan State University

[Return to the Organic Home Page](#)

[NCMS Solvent
Database](#)

CUBoulder Organic Chemistry Undergraduate Courses



Lab Techniques

Crystallization

- [Study Questions/Answers from the Handbook for Organic Chemistry Lab](#)

Crystallization is a technique which chemists use to purify solid compounds. It is one of the fundamental procedures each chemist must master to become proficient in the laboratory. Crystallization is based on the principles of solubility: compounds (solutes) tend to be more soluble in hot liquids (solvents) than they are in cold liquids. If a saturated hot solution is allowed to cool, the solute is no longer soluble in the solvent and forms crystals of pure compound. Impurities are excluded from the growing crystals and the pure solid crystals can be separated from the dissolved impurities by filtration.

This simplified scientific description of crystallization does not give a realistic picture of how the process is accomplished in the laboratory. Rather, successful crystallization relies on a blend of science and art; its success depends more on experimentation, observation, imagination, and skill than on mathematical and physical predictions. Understanding the process of crystallization in itself will not make a student a master crystallizer, rather, this understanding must be combined with laboratory practice to gain proficiency in this technique.

How to do a crystallization

To crystallize an impure, solid compound, add just enough hot solvent is added to it to completely dissolve it. The flask then contains a hot solution, in which solute molecules – both the desired compound and impurities – move freely among the hot solvent molecules. As the solution cools, the solvent can no longer “hold” all of the solute molecules, and they begin to leave the solution and form solid crystals. During this cooling, each solute molecule in turn approaches a growing crystal and rests on the crystal surface. If the geometry of the molecule fits that of the crystal, it will be more likely to remain on the crystal than it is to go back into the solution. Therefore, each growing crystal consists of only one type of molecule, the solute. After the solution has come to room temperature, it is carefully set in an ice bath to complete the crystallization process. The chilled solution is then filtered to isolate the pure crystals and the crystals are rinsed with chilled solvent.

Detailed photos from start to finish.

- [crystallization procedure](#)

Crystallization Movie. To view this movie, you need the RealOne movie player. If you do not have this installed in your browser, go to www.real.com and click on the box in the upper right hand corner that says "free download". Streaming video works best if you are on the University campus; if you are using a dialup modem, the quality is acceptable but not great.

Slow vs rapid cooling in a crystallization

Diagrams showing what happens when you cool too fast.

- [cooling](#)

Close-up of pictures forming in a flask

<http://orgchem.colorado.edu/hndbksupport/cryst/cryst.html>

5/24/2005

- [crystals forming, time-lapse](#)

Pictures of some really pretty crystals

- [Diels-Alder crystals 1](#)
- [Diels-Alder crystals 2](#)
- [Diels-Alder crystals 3](#)

[to](#)
[Lab Techniques](#)
[Contents](#)

[Lecture Courses](#) | [Lab Courses](#) | [Organic Chemistry Lab Topics](#) | [Links](#)

[email the webmaster](#)

[Organic Courses](#)
[Home](#)